REMARKS

Claims 30, 31, 35, 38, and 39 have been amended. Claims 46-49 have been cancelled. New claims 50-55 have been added. Claims 30-45 and 50-55 are pending in the present application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. Objections to the Specification

The specification is objected to because figure 4 is not labeled "Fig 4". Correction was requested. Attached is a new Figure 4 labeled as "Fig. 4A" and "Fig. 4B".

The specification is also objected to for misspelling, throughout the specification, the name "Svendsen". Applicant has carefully reviewed the specification and determined that "Svendsen" is properly spelled on page 42, line 4, page 48, line 6, and page 48, line 8.

II. The Rejection of Claims 35 and 39 under 35 U.S.C. § 112, Second Paragraph

Claims 35 and 39 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on two grounds.

Ground 1: The Office Action states that claim 35 is indefinite because claim 35 recites "The nucleic acid sequence of claim 34, which encodes a polypeptide consisting of amino acids 19-555 of SEQ ID NO: 2, while claim 34 recites "The nucleic acid sequence. . ., which encodes a polypeptide consisting of the amino acid sequence of SEQ ID NO: 2". The Office Action suggests that since the nucleic acid sequence of claim 35 cannot consist of a molecule wherein residues 1-18 are simultaneously present and not present, that applicants amend claim 35 to depend from claim 33, which includes fragments of SEQ ID NO: 2. Claim 35 has been amended to depend from claim 33.

Ground 2: The Office Action states that Claim 39 is indefinite for reciting "high stringency" on line 2 and "wherein medium stringency conditions are..." on line 4. Claim 39 has been amended to recite "high stringency" on line 4.

For the foregoing reasons, Applicants submit that the new claims overcome the rejections under 35 U.S.C. § 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 30, 31, 36, 38, 40, and 42-49 under 35 U.S.C. § 112, First Paragraph

Claims 30, 31, 36, 38, 40, and 42-49 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for isolated nucleic acid molecules encoding SEQ ID NO: 2 or fragments thereof having carboxypeptidase activity, does not reasonably provide enablement for any nucleic acid molecule (i) encoding any protein having at least 70% identity with residues 19-555 of SEQ ID NO: 2, (ii) having at least 70% identity with SEQ ID NO: 1 or residues 55-1662 of SEQ ID NO: 1, (iii) which hybridizes under medium stringency with residues 55-1662 of SEQ ID NO: 1, or at least 100 nucleotides thereof, or the complement thereof, (iv) encoding a polypeptide having carboxypeptidase activity with optimal activity in the pH range of 4-5, in the temperature range of 55°-60°C, with residual activity of 65% after 30 minutes, and the ability to hydrolyze Phe from N-CBZ-Ala-Phe, or (v) encoding the polypeptide of (iv), wherein the polynucleotide is from a strain of *Aspergillus*. This rejection is respectfully traversed.

The present invention relates to isolated nucleic acid sequences encoding a polypeptide having carboxypeptidase activity, selected from the group consisting of:

(a) a nucleic acid sequence encoding a polypeptide having an amino acid sequence which has at least 80% identity with amino acids 19 to 555 of SEQ ID NO. 2;

(b) a nucleic acid sequence having at least 80% homology with nucleotides 55 to 1662 of SEQ ID NO. 1; and

(c) a nucleic acid sequence which hybridizes under medium stringency conditions with nucleotides 55 to 1662 of SEQ ID NO. 1, or its complementary strand, wherein medium stringency conditions are defined as prehybridization and hybridization a 42°C in 5X SSPE, 0.3% SDS, 200 mg/ml sheared and denatured salmon sperm DNA, and 35% formamide

It is well settled that "[t]he first paragraph of section 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). Moreover, "a specification disclosure which contains a teaching of the manner and process of

making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 USPQ at 369.

The reasoning provided in the Office Action is that the specification does not establish the regions of protein structure which may be modified without effecting carboxypeptidase activity and the general tolerance of a polypeptide having carboxypeptidase activity to modification and extent of such tolerance. Applicants respectfully submit that this reasoning is not sufficient to render the claims nonenabled.

The claimed nucleic acid sequences are structurally similar because they encode a polypeptide having an amino acid sequence that is at least 80% identical with the amino acids 19 to 555 of SEQ ID NO. 2, they have at least 80% homology with nucleotides 55 to 1662 of SEQ ID NO. 1, or they hybridize under at least medium stringency conditions with nucleotides 55 to 1662 of SEQ ID NO. 1 or its complementary strand. One of ordinary skill in the art would, therefore, expect that the claimed nucleic acids encode polypeptides having carboxypeptidase activity.

Furthermore, Applicants have provided detailed methods for isolating the claimed nucleic acid sequences and determining whether they fall within the scope of protection sought by Applicants. Applicants describe methods for preparing and probing DNA libraries (Example 4-7); for isolating nucleic acids encoding the carboxypeptidases (Example 7); for determining cross-hybridization of the nucleic acids encoding carboxypeptidases using nucleotides 55 to 1662 of SEQ ID NO: 1, or their complementary nucleotides (Example 9); for comparing the percent identity of the deduced amino acid sequences of the carboxypeptidases to amino acids 19 to 555 of SEQ ID NO: 2 using the Clustal method according to Higgins, 1989, *CABIOS* 5: 151-153 (Example 8); for determining the degree of homology between two nucleic acid sequences using the Clustal method according to Higgins, 1989, *supra* (page 12, lines 14-20); for producing the carboxypeptidases (page 26, line 26, to page 27, line 24); and for purifying the carboxypeptidases and characterizing the properties of the encoded carboxypeptidases (Examples 1-3). Applicants assert that it is well within the skill of the art to isolate and identify the claimed nucleic acid sequences using the Applicants' disclosure.

Moreover, Applicants disagree with the Office's statement that "it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims...." Companies which develop enzymes are able to produce and screen thousands of enzymes in a short period of time. Indeed, enzymes companies have developed automated robotic systems for producing and screening enzymes. See, for example, Michael Lamsa, Nils Buchberg Jensen, and Steen Krogsgaard, Screen Automation and Robotics, *in* Enzyme Functionality, Design, Engineering, and Screening (Allan Svendsen ed., Marcel Dekker 2003), pp. 527-559.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. The Rejection of Claim 41 under 35 U.S.C. § 112, First Paragraph

Claim 41 stands rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Specifically, the Office Action requested a declaration that NRRL B-21616 is readily available to the public.

As requested, Applicants enclose a Statement under 37 C.F.R. § 1.808 that the strain was deposited under the Budapest Treaty and all restrictions will be removed upon the granting of the U.S. patent. Applicants therefore submit that this rejection has been overcome.

V. The Rejection of Claims 30, 31, 36, 38, 40, and 42-49 under 35 U.S.C. § 112, First Paragraph

Claims 30, 31, 36, 38, 40, and 42-49 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action stated:

> These claims are directed to a genus of nucleic acid molecules ... The specification teaches the structure of only a single representative species of such polynucleotides, SEQ ID NO: 1. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the ability to hybridize under medium stringency with residues 55-1662 of SEQ ID NO: 1, or at least 100 nucleotides or the complement thereof, and encoding a carboxypeptidase, or encoding polypeptides having carboxypeptidase activity with optimal activity in the pH range of 4-5, in the temperature range of

> 55°-60°C, with residual activity of 65% after 30 minutes, and the ability to hydrolyze Phe from N-CBZ-Ala-Phe. The genus of nucleic acid molecules having the recited structural feature of the genus (i.e., the ability to hybridize under medium stringency with residues 55-1662 of SEQ ID NO: 1, or at least 100 nucleotides or the complement thereof) is a large and variable genus and those species encoding a carboxypeptidase do not constitute a substantial portion of said genus of nucleic acid molecules. Furthermore the structure of the genus of polynucleotides encoding polypeptides with carboxypeptidase activity and having optimal activity in the pH range of 4-5, in the temperature range of 55°-60°C, with residual activity of 65% after 30 minutes, and the ability to hydrolyze Phe from N-CBZ-Ala-Phe is completely undefined.

This rejection is respectfully traversed.

Applicants submit that the specification complies with the written description requirement.

It is well settled "[t]he test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter ..." *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983).

As set forth in Federal Circuit decisions, a specification complies with the written description requirement if it provides "a precise definition, such as by structure, formula, chemical name, or physical properties of the claimed subject matter sufficient to distinguish it from other materials." See, e.g., *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997); *Enzo Biochem v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). In fact, "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Eli Lilly and Co.*, 43 U.S.P.Q.2d at 1569. The test is not whether one of ordinary skill in the art envisions all of the claimed subject matter, as suggested in the Office Action.

Claims 30, 31, 36, 38, and 40 are drawn to nucleic acid sequences encoding polypeptide that have carboxypeptidase activity. Claims 46-49 have been canceled. The claimed nucleic acid sequences are structurally similar because of the structural features that they encode a polypeptide having an amino acid sequence that is at least 80% identical with the amino acids 19 to 555 of SEQ ID NO. 2, they have at least 80% homology with nucleotides 55 to 1662 of SEQ ID NO. 1, or they hybridize under at least medium stringency conditions with nucleotides 55 to 1662 of SEQ ID NO. 1 or its complementary strand. Thus, the specification provides a

precise definition of the claimed nucleic acid sequences and claims 30, 31, 36, 38, and 40 comply with the written description requirement.

Claim 42 is drawn to a nucleic acid construct. The specification on page 14, line 1, to page 20, line 3, describes nucleic acid constructs. Thus, the specification provides a precise definition of nucleic acid constructs and claim 42 fully complies with the written description requirement.

Claim 43 is drawn to a recombinant expression vector. The specification on page 20, line 5, to page 22, line 24, describes recombinant expression vectors. Thus, the specification provides a precise definition of recombinant expression vectors and claim 43 fully complies with the written description requirement.

Claim 44 is drawn to a recombinant host cell. The specification on page 22, line 26, to page 26, line 24, describes recombinant host cells. Thus, the specification provides a precise definition of recombinant host cells and claim 44 fully complies with the written description requirement.

Claim 45 is drawn to a method of producing a polypeptide having carboxypeptidase activity with such a host cell. The specification on page 26, line 26, to page 28, line 2, describes methods of production. Thus, the specification provides a precise definition of methods of producing a polypeptide having carboxypeptidase activity and claim 45 fully complies with the written description requirement.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

VI. The Rejection of Claims 30, 40, 46, and 47 under 35 U.S.C. § 103

Claims 30, 40, 46, and 47 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Svendsen *et al.* (*FEBS Letters* 333: 39-43, 1993), as evidenced by Hoffman *et al.* (*Methods in Enzymology* 45: 587-599, 1976), in view of Metzler *et al.* (Biochemistry: The Chemical Reactions of Living Cells, Academic Press, New York, New York, 1977, page 901). The Office Action states:

> Svendsen *et al.*, teach the amino acid sequence of a carboxypeptidase previously characterized by Hoffman *et al.* As shown by Hoffman *et al.*, said carboxypeptidase has optimal activity at pH 4.3 (p 597, parg 4) and is stable at pH 4 for prolonged times (p 593, parg 1). The carboxypeptidase of Hoffman *et al.* can hydrolyze N-CBZ-Ala-Ala (Table III), as well as cleaving terminal isoleucine, glutamic acid, lysine, arginine, aspartic acid, asparagine,

> phenyalanine, and tyrosine residues from peptides (Table IV). Although Svendsen *et al.* teach the amino acid sequence of the carboxypeptidase, they do not teach the polynucleotide sequence encoding the carboxypeptidase. However, the polynucleotide sequences encoding any known polypeptide sequence can be deduced from the genetic code, as taught by Metzler *et al.* It would have been obvious to a person of ordinary skill in the art to use the genetic code to deduce all the nucleic acid sequences that can encode the polypeptide of Svendsen *et al.* Motivation to do so derives from the advantage of using said deduced sequences to produce the carboxypeptidase of Svendsen *et al.* The advantages of recombinant production of proteins are well known in the art.

This rejection is respectfully traversed.

Preliminarily, claims 46-49 have been canceled.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 US 1 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. *In re Stencel*, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987).

A prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein. *In re Bell*, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993).

Svendsen *et al.* disclose the complete amino acid sequence of carboxypeptidase S1 from *Penicillium janthinellum*.

Hoffman *et al.* disclose the isolation, purification, and properties of carboxypeptidases S1 and S2 from *Penicillium janthinellum*, termed penicillocarboxypeptidases S-1 and S-2.

Metzler *et al.* disclose the deciphering of the genetic code.

However, Swendsen *et al.*, Hoffman *et al.*, or Metzler *et al.*, alone or in combination, do not teach or suggest an isolated nucleic acid sequence encoding a polypeptide having carboxypeptidase activity, selected from the group consisting of: (a) a nucleic acid sequence encoding a polypeptide having an amino acid sequence which has at least 80% identity with amino acids 19 to 555 of SEQ ID NO. 2; (b) a nucleic acid sequence having at least 80%

homology with nucleotides 55 to 1662 of SEQ ID NO. 1; and (c) a nucleic acid sequence which hybridizes under medium stringency conditions with nucleotides 55 to 1662 of SEQ ID NO. 1, or its complementary strand, as claimed herein. Moreover, using the Clustal alignment program (Higgins, 1989, *CABIOS* 5: 151-153) to compare the deduced amino acid sequence of the *Aspergillus oryzae* ATCC 20386 carboxypeptidase I to the deduced amino acid sequence of the *Penicillium janthinellum* carboxypeptidase S1, only a 38.8% identity was observed.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. § 103(a). Applicants respectfully request reconsideration and withdrawal of the rejection.

VII. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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